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Neuromechanical assessment of knee joint instability during perturbed gait in patients with knee osteoarthritis

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ABSTRACT

Knee joint instability is frequently reported by patients with knee osteoarthritis (KOA). Objective metrics to assess knee joint instability are lacking, making it difficult to target therapies aiming to improve stability. Therefore, the aim of this study was to compare responses in neuromechanics to perturbations during gait in patients with self-reported knee joint instability (KOA-I) versus patients reporting stable knees (KOA-S) and healthy control subjects.

Forty patients (20 KOA-I and 20 KOA-S) and 20 healthy controls were measured during perturbed treadmill walking. Knee joint angles and muscle activation patterns were compared using statistical parametric mapping and discrete gait parameters. Furthermore, subgroups (moderate versus severe KOA) based on Kellgren and Lawrence classification were evaluated.

Patients with KOA-I generally had greater knee flexion angles compared to controls during terminal stance and during swing of perturbed gait. In response to deceleration perturbations the patients with moderate KOA-I increased their knee flexion angles during terminal stance and pre-swing. Knee muscle activation patterns were overall similar between the groups. In response to sway medial perturbations the patients with severe KOA-I increased the co-contraction of the quadriceps versus hamstrings muscles during terminal stance.

Patients with KOA-I respond to different gait perturbations by increasing knee flexion angles, co-contraction of muscles or both during terminal stance. These alterations in neuromechanics could assist in the assessment of knee joint instability in patients, to provide treatment options accordingly. Furthermore, longitudinal studies are needed to investigate the consequences of altered neuromechanics due to knee joint instability on the development of KOA.

1. Introduction

Knee osteoarthritis (KOA) is a highly prevalent joint disease causing pain and disability for the patient (Cross et al., 2014; Hawker, 2019). A large group (~65%) of these patients report having knee joint instability during dynamic daily activities such as gait (Fitzgerald et al., 2004; Leichtenberg et al., 2018; van der Esch et al., 2012). While knee joint instability is associated with increased pain and decline of physical function (Farrokhi et al., 2015; Fitzgerald et al., 2004; Leichtenberg et al., 2018; van der Esch et al., 2012), it also may play a role in the initiation and progression of KOA (Blalock et al., 2015a; Egloff et al., 2016; Kamekura et al., 2005). Treatment options to improve knee joint stability could be available (i.e. muscle strengthening (Knoop et al., 2014, 2013), braces (Cudejko et al., 2017; Ramsey et al., 2007), but a clinically accepted objective measure for knee joint stability is lacking making it difficult to target these treatments (Farrokhi et al., 2014; Schrijvers et al., 2019; Wallace et al., 2019). Current methods used to objectively assess knee joint instability such as laxity measurements were shown not to be related with self-reported knee joint instability (Knoop et al., 2012; Schmitt et al., 2008). A reason for this could be that laxity measurements do not fully capture knee joint instability during daily activities, which is a combination of

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the passive system (i.e. ligaments, joint capsule) and active system (muscle activations) (Schipplein and Andriacchi, 1991). Therefore, development of an objective measurement of knee joint instability during dynamic activities is needed that is related to perceived knee joint instability. This will assist in selecting a more personalized treatment per patient and early identification of individuals that are at risk of developing knee joint instability.

Objective parameters of gait analysis are frequently used to assess knee function in patients with knee osteoarthritis (Favre and Jolles, 2016). Several attempts have been made to measure knee joint instability during gait, but without compelling evidence (Schrijvers et al., 2019). This was mainly due to absence of a clear definition for dynamic knee joint stability and the inability to compare studies, because of differences in gait analysis protocols (Schrijvers et al., 2019). A conceptual definition for dynamic knee joint stability was previously suggested by us: "The capacity to respond to a challenge during gait within the natural boundaries of the knee" (Schrijvers et al., 2019). We believe that a challenge (e.g. perturbation) during gait is needed to evoke the episodes of knee joint instability that patients experience in daily life. Furthermore, the capacity to respond to such a challenge with adaptive neuromechanics (knee movements and muscle activation) could differentiate patients with knee joint instability from those with stable knees, whereas the healthy control subjects of similar age sets the boundaries of a natural response to such a challenge. As far as we know, one study dichotomized patients with KOA into patients with self-reported knee joint instability (KOA-I) versus patients reporting stable knee joints (KOA-S) during perturbed gait (Schmitt and Rudolph, 2008). This study showed similar biomechanics between the groups and higher co-contraction of medial muscles in patients with KOA-I (Schmitt and Rudolph, 2008). Other studies investigating perturbed gait (sway lateral or medial perturbations) in patients with KOA observed no differences in knee biomechanics and muscle activation patterns compared to healthy controls (Baker et al., 2019; Kumar et al., 2014). The absence of differences between patients with KOA and healthy controls may be due to the limited number of perturbation types investigated. Furthermore, the severity of KOA was also not taken into account (Favre et al., 2014; Huang et al., 2008). Therefore, the aim of this study is to compare responses in neuromechanics to perturbations during gait in patients with KOA-I versus patients with KOA-S and healthy control subjects.

2. Methods

2.1. Subjects

Forty patients with KOA were recruited from the patient database of the Amsterdam UMC, location Vrije Universiteit Amsterdam (VUmc) (Richards et al., 2018) or Amsterdam osteoarthritis (AMS-OA) cohort of Reade (Knoop et al., 2012), centre of rehabilitation and rheumatology, Amsterdam, the Netherlands (Table 1). Inclusion criteria were (1) clinical diagnose of KOA according to clinical American College of Rheumatology criteria (Altman et al., 1986), (2) maximal score of 7 on the numeric pain rating scale (Hawker et al., 2011)) during the past 2 weeks, (3) able to walk for 5 min without stopping and (4) body mass index (BMI) between 20 and 35 kg/m^2. Exclusion criteria were (1) diagnosis of hip osteoarthritis, rheumatoid arthritis or any other form of inflammatory arthritis, (2) knee injury last year, (3) lower extremity joint replacement and (4) not willing to walk without walking aid. The patients were assigned to the 'instability' group (KOA-I, n = 20) if they have had the perception of instability (episode of buckling, shifting or giving way) of the knee in the past 4 weeks, otherwise they were assigned to the 'stability' group (KOA-S, n = 20) (Felson et al., 2007; Leichtenberg et al., 2017; van der Esch et al., 2012). Group sizes were based on a power analysis with knee kinematics and electromyography as outcome measures (power of 80%, significance level of 0.05) (Granata et al., 2005; McGinley et al., 2009).

The healthy control subjects were age-, gender- and BMI-matched with the KOA group. Exclusion criteria were (1) diagnosis of a musculoskeletal disease, (2) knee injury in the past five years, (3) lower extremity joint replacement and (4) knee-related problems (e.g. instability, pain). All subjects provided written informed consent. This study was approved by the medical ethics committee of the Amsterdam UMC, location VUmc.

2.2. Measurement protocol

The measurements were performed in the gait laboratory (Virtual Reality lab) of the rehabilitation medicine department of the Amsterdam UMC, location VUmc. This laboratory (GRAIL system, Motekforce Link BV, Amsterdam, the Netherlands) contains a dual-belt instrumented treadmill able to execute perturbations in

Table 1
Subject characteristics and spatiotemporal parameters (average of all perturbed strides independent of perturbation type or intensity). NA = Not applicable.

	KOA-I (n = 20)	KOA-S (n = 20)	Control (n = 20)	p-value
Age (years)	65 ± 7	68 ± 9	65 ± 6	0.22
Female (n)	13 (65%)	11 (55%)	11 (55%)	0.76
Weight (kg)	81 ± 17	81 ± 12	75 ± 13	0.77
Height (cm)	177 ± 10	177 ± 10	175 ± 8	0.25
Body mass index (kg/m^2)	26 ± 4	26 ± 2	24 ± 4	0.33
K&L grade (n)			NA	0.61
0	0 (0%)	1 (5%)	-	
1	3 (15%)	5 (25%)	-	
2	9 (45%)	5 (25%)	-	
3	2 (10%)	2 (10%)	-	
4	6 (30%)	7 (35%)	-	
Walking speed (m/s)	1.28 (0.25)	1.30 (0.20)	1.40 (0.20)	0.05[nn]
Stride time (s)	1.01 (0.09)	0.99 (0.09)	0.98 (0.08)	0.56
Stance time (s)	0.67 (0.07)	0.66 (0.07)	0.65 (0.06)	0.51
Swing time (s)	0.34 (0.03)	0.33 (0.03)	0.33 (0.02)	0.44
Stance (%)	66	67	66	0.25
Swing (%)	34	33	34	0.25
Stride length (m)	1.23 (0.19)	1.24 (0.20)	1.33 (0.17)	0.22
Step length (m)	0.58 (0.11)	0.61 (0.11)	0.65 (0.07)	0.17[nn]
Step width (m)	0.14 (0.03)	0.15 (0.06)	0.13 (0.03)	0.51[nn]

Results are presented as mean (standard deviation) or when not normally distributed ([nn]) as median (interquartile range), except for gender and K&L grades which are presented as number of subjects and percentage.

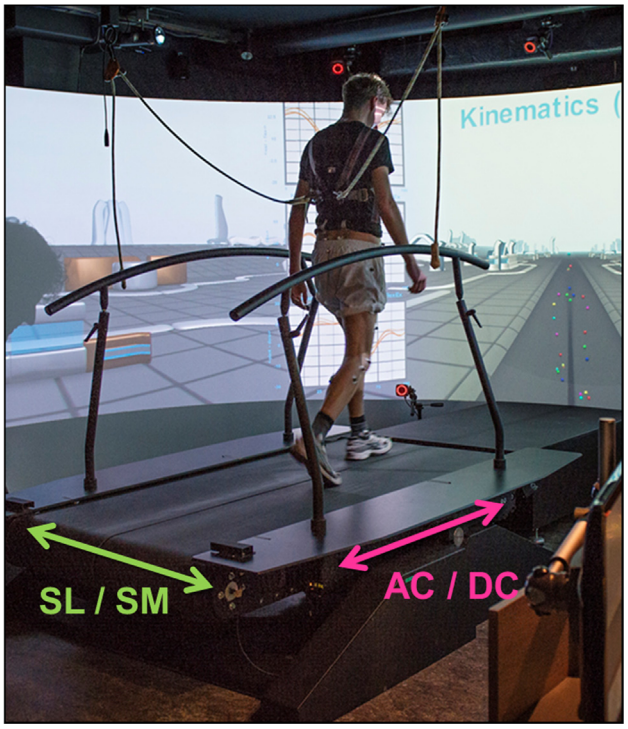

Fig. 1. Overview of the measurement setup and the four perturbation types that can be applied by the GRAIL system. AC: acceleration of one belt, DC: deceleration of one belt, SL: sway lateral and SM: sway medial. Sway Lateral was defined as a sway to the left if the affected leg was left and a sway to the right if the affected leg was right.

four directions (Fig. 1). Furthermore, it contains a virtual reality environment, ten motion capture cameras (VICON, Oxford, United Kingdom), surface electromyography (EMG) recording (Cometa, Milan, Italy) and the necessary safety equipment (i.e. safety harness).

Each measurement started with obtaining subject specific characteristics (i.e. age, BMI, sex, most affected leg). Next, the subject was prepared for walking on the treadmill by placing reflective markers and EMG electrodes on pre-specified places (calibrated anatomical systems technique (CAST) marker model (Cappozzo et al., 1995), SENIAM EMG placement protocol (Hermens et al., 2000)). First, a four-minute warm-up walking trial was performed wherein the comfortable walking speed of the subject was determined. Subsequently, a four-minute unperturbed walking trail was recorded. After this, four perturbed walking trails (four minutes each) were performed using the perturbation protocol described below. In addition, X-rays of the knee joint were made using the Buckland-Wright protocol (Buckland-Wright et al., 2003).

2.3. Perturbation protocol

Each perturbed walking trial consisted of twelve different perturbations (four types, each with three intensities) applied in a random order to the subject with at least seven strides in-between for the subject to recover. Perturbations were triggered by initial contact of the most affected leg (this leg was chosen with a random generator for the healthy controls). The perturbation types tested were acceleration of one belt (ACC), deceleration of one belt (DEC), sway medial (SM) and sway lateral (SL) (Fig. 1). The intensities ranged from 0.7 to 1.6 m/s for the ACC and DEC perturbations (change in walking speed in 10–20 ms) and 2–4 cm for the SM and SL perturbations (Fig. 2). Perturbations will be abbreviated by type and intensity in the tables and figures, for example sway lateral at intensity 2 becomes SL2.

2.4. Data analysis

2.4.1. Kinematics

Motion capture (100 Hz) data was inputted into a custom-made Matlab program ('BodyMech', Amsterdam UMC, location VUmc) to yield three-dimensional knee joint angles, using the anatomical coordinate systems of Cappozzo et al. (Cappozzo et al., 1995) and joint coordinate systems of Grood and Suntay (Grood and Suntay, 1983). The obtained knee angles were time-normalized to percentage gait cycle using a cubic interpolation function and marker-based initial contacts and toe-offs (Zeni et al., 2008) (using pelvis and heel markers). The strides of the unperturbed walking trial were ensemble-averaged over about 60 strides per subject. The perturbed strides of the perturbed walking trials were ensemble-averaged over 4 strides per perturbation type, intensity and subject. Subsequently, the strides were averaged over subjects to obtain the group average pattern. Common discrete gait parameters (peak, initial contact, range of motion (ROM) values) were calculated from the ensemble-averaged knee joint angles of the affected leg of each subject. Furthermore, spatiotemporal parameters were calculated using heel marker kinematics, walking velocity and the initial contacts and toe-offs.

2.4.2. Muscle activation

EMG was recorded (1000 Hz) of the vastus lateralis (VL), vastus medialis (VM), rectus femoris (RF), lateral hamstring (LH), medial hamstring (MH), lateral gastrocnemius (LG), medial gastrocnemius (MG) and gluteus medius (GM). To obtain the EMG envelopes, the signals were one-way high-pass filtered (20 Hz, 3rd order, Butterworth), rectified and two-way low-pass filtered (2 Hz, 4th order, Butterworth). The EMG envelopes were divided into strides using the previously described time-normalization method. Furthermore, the amplitude of the EMG envelopes was expressed as a percentage of peak activation that occurred during the unperturbed strides. The strides of the unperturbed walking trial were ensemble-averaged over about 60 strides per subject. The perturbed strides of the perturbed walking trials were ensemble-averaged over 4 strides per perturbation type, intensity and subject. Subsequently, the strides were averaged over subjects to obtain the group average pattern. Discrete gait parameters (initial contact and mean values) were calculated of the ensemble-averaged muscle activation patterns of the affected leg of each subject. Additionally, co-contraction indices (CCI) of the lateral side (VM and MH), medial side (VL and LH) and total of the knee (VM, RF, VL and MH, LH) were calculated according to the following equation (Eqn 1):

$$CCI(i) = 1 - \frac{|EMG_{ag}(i) - EMG_{ant}(i)|}{EMG_{ag}(i) + EMG_{ant}(i)} \quad (1)$$

$EMG_{ag}(i)$ represents the muscle activity of the agonist muscle and $EMG_{ant}(i)$ the muscle activity of the antagonist muscle at each time point (i) of the gait cycle. The CCI(i) was calculated for each time point separately, as well as the mean value over full gait cycle. A CCI = 0 indicates no co-contraction and CCI = 1 indicates full co-contraction (Doorenbosch et al., 1995).

2.4.3. Perturbation response

The perturbation response was used to capture the response of the subject in a gait parameter (e.g. knee flexion angle or rectus femoris activation) to a perturbation (Hobbelen and Wisse, 2007; van den Noort et al., 2017). The perturbation response was calculated with the following equation (Eqn 2):

$$PR(i) = \sqrt{\left(\frac{\mu_p(i) - \mu(i)}{SD(i)}\right)^2} \quad (2)$$

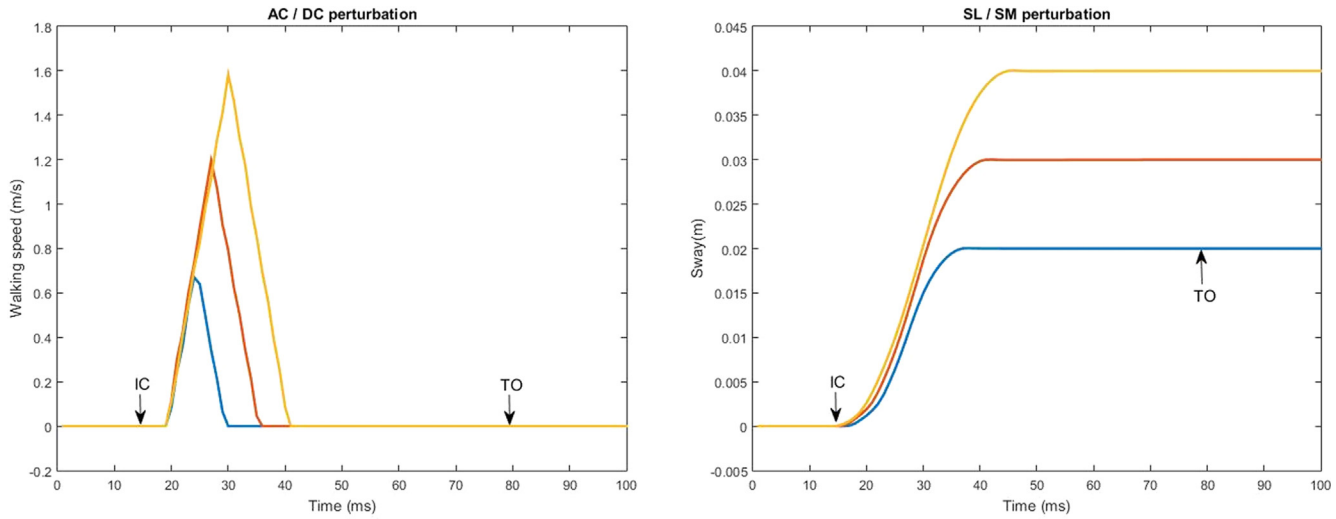

Fig. 2. Specifications of the perturbation types and intensities applied to the subject. Intensity 1 is the blue line, intensity 2 the red line and intensity 3 the yellow line. IC: initial contact, TO: toe off, AC: acceleration of one belt, DC: deceleration of one belt, SL: sway lateral and SM: sway medial.

The $\mu_p(i)$ represents the mean of the chosen gait parameter at a certain time point (i) of the gait cycle during perturbed walking. For the same time point (i) the mean of the chosen gait parameter was calculated during unperturbed walking $\mu(i)$. The difference between the means ($\mu_p(i)$- $\mu(i)$) is divided by the standard deviation of the gait parameter at time point (i) during unperturbed walking. The absolute number that remains is the perturbation response PR(i) at time point (i). This number represents the variability of the selected gait parameter in response to a perturbation at a certain time point of the gait cycle taking into account the naturally occurring variability during unperturbed walking. A higher perturbation response therefore indicates more variability in the gait parameter caused by the perturbation.

2.4.4. Radiographic severity

The obtained X-rays were scored by an experienced assessor using the Kellgren and Lawrence classification system (K&L) (Kellgren and Lawrence, 1957). Moderate KOA was defined as patients that scored 2 or lower and severe KOA was defined as patients that scored higher than 2 (Favre et al., 2014; Huang et al., 2008).

2.5. Statistical analysis

Descriptive statistics were calculated of the subject characteristics, spatiotemporal gait parameters and discrete gait parameters derived from the knee joint angles and muscle activation patterns, for each (sub) group separately.

Sex and K&L grades were compared between the groups using the Chi-square test. The other subject characteristics and spatiotemporal parameters were tested for normality with the Shapiro-Wilk test. If normally distributed, a multivariate analysis was used with post-hoc pairwise comparisons (with Bonferroni correction) to compare the groups. If not normally distributed, the subject characteristics and spatiotemporal gait parameters were compared using a non-parametric test (Mann-Whitney U or Kruskal-Wallis 1-way ANOVA).

Statistical parametric mapping analysis (Friston et al., 1994) and discrete gait parameters were used to compare knee angles, muscle activation patterns, CCI and perturbation responses of the groups. In the statistical parametric mapping analysis, a one-way ANOVA was used to identify phases of gait that were different between the groups. Mean values over these phases of gait, as well as the discrete gait parameters were then tested for normality using the Shapiro-Wilk test. If normally distributed, the groups were compared using a multivariate analysis (covariate: walking velocity) and post-hoc pairwise comparisons (with Bonferroni correction). If not normally distributed, the mean values and discrete gait parameters were checked for skewness and transformed, if necessary, by a square root transformation. If the square root transformation was not sufficient to minimize skewness, a log transformation was used instead. Hereafter, the same multivariate analysis was performed as for the normally distributed values and parameters. The significance level was $\alpha < 0.05$.

3. Results

3.1. KOA-I vs. KOA-S and control

No differences were present in age, sex or BMI between the groups. Both KOA groups had similar distribution of radiographic disease severity ($p = 0.61$). Furthermore, the spatiotemporal parameters did not differ between the groups (Table 1). One control subject was excluded from the group for the biomechanical analysis, because of kinematic outliers (above three times the standard deviation of the total group).

The statistical parametric mapping analysis of knee angles showed only differences between the groups in the knee flexion angles during terminal stance and (pre-)swing of the perturbed stride and stride after perturbation (Fig. 3). For example, patients with KOA-I had greater flexion angles during 45–51% and 188–195% of gait cycle in response to the acceleration of one belt perturbation at intensity 3 compared to healthy controls (mean difference: 7.9°, $p = 0.01$, mean difference: 6.9°, $p < 0.01$), and during 175–184% of gait cycle compared to patients with KOA-S and healthy controls (mean difference: 4.6°, $p < 0.01$). Details on all statistical parametric mapping analysis results are presented in supplementary Table A. In line with the results of the statistical parametric mapping analysis, the comparison of the discrete gait parameters mainly showed higher knee flexion angles during peak terminal stance (maximum knee extension around 40–50% gait cycle) and peak swing in patients with KOA-I compared to healthy controls and patients with KOA-S for peak swing (Table 2 and supplementary Table B and D).

The muscle activation patterns in response to the perturbations were similar between the groups (statistical parametric mapping analysis results in supplementary table A). Only few alterations

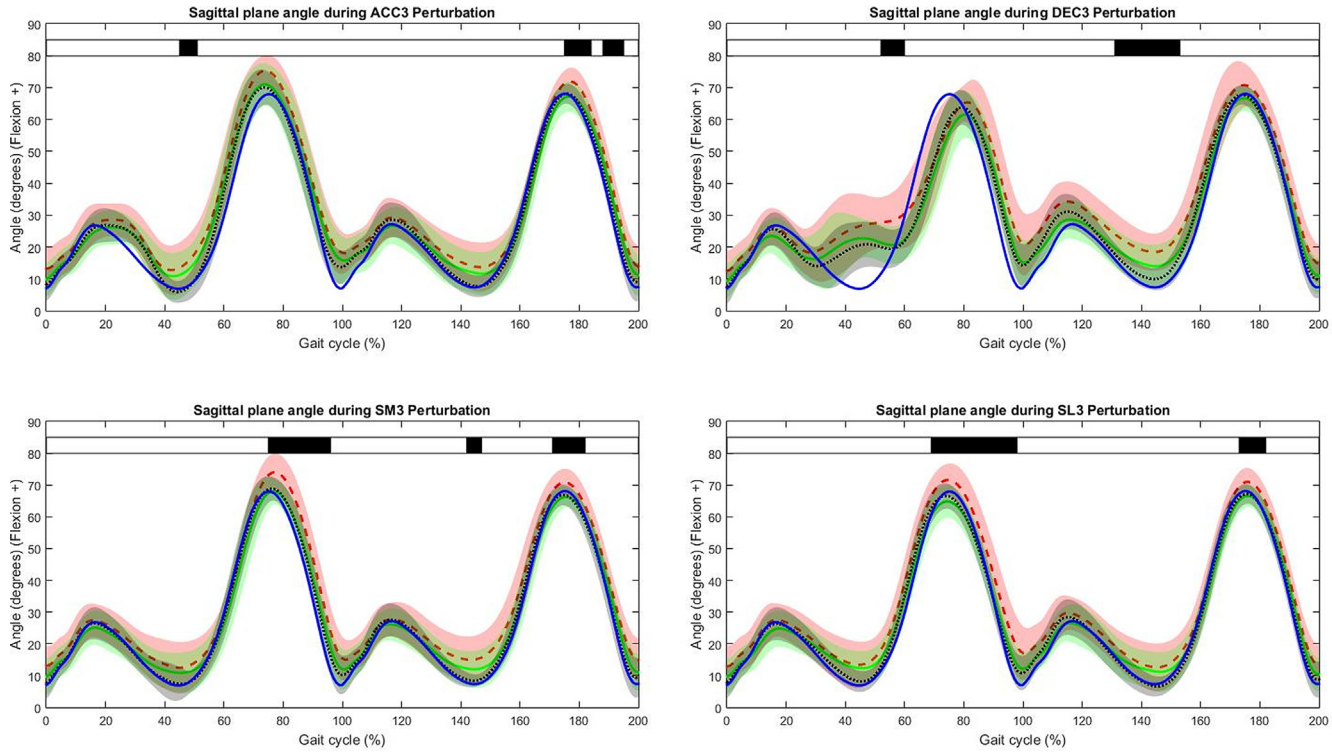

Fig. 3. Sagittal plane angles (Knee flexion angles) of perturbed stride and stride after perturbation during the ACC, DEC, SM and SL perturbation intensity 3. KOA-I group (red, dashed line), KOA-S group (green, solid line) , healthy control group perturbed (black, dotted line) and healthy control group unperturbed (blue solid line). The line represents the mean pattern of the group and the shaded area represents the standard deviation of the patterns of the group. Rectangle above graph shows significant differences (black) or not (white) between groups following from the SPM results. The control group unperturbed (blue line) was not used in the SPM analysis.

Table 2
Significant differences between the groups (KOA-I, KOA-S and Control) in the discrete gait parameters of the perturbed stride of the four different perturbation types at intensity 3. ROM = Range of motion.

Acceleration of one belt (ACC3)				
Parameter		***Groups***	***Mean difference***	***p- value***
Sagittal plane angle	Peak terminal stance	KOA-I vs. Control	+6.4°	0.03
	Peak swing	KOA-I vs. Control	+5.5°	<0.01
Frontal plane angle	ROM full gait cycle	KOA-S vs. Control	+3.8°	0.04
Gluteus medius	Peak activation	KOA-S vs. KOA-I	+43%	<0.01
		KOA-S vs. Control	+33%	0.04
Deceleration of one belt (DEC3)				
Sagittal plane angle	Peak swing	KOA-I vs. KOA-S	+5.1°	0.02
		KOA-I vs. Control	+3.9°	0.03
Sway Medial (SM3)				
Sagittal plane angle	Peak swing	KOA-I vs. KOA-S	+5.4°	<0.01
		KOA-I vs. Control	+4.8°	<0.01
	ROM full gait cycle	KOA-I vs. KOA-S	+4.5°	0.05
Sway Lateral (SL3)				
Sagittal plane angle	Peak swing	KOA-I vs. KOA-S	+6.9°	<0.01
		KOA-I vs. Control	+5.2°	<0.01
	ROM full gait cycle	KOA-I vs. KOA-S	+6.2°	<0.01

were observed in the discrete gait parameters of the muscle activation patterns (Table 2 and supplementary table C and E).

3.2. Subgroup analysis

The subject characteristics and spatiotemporal parameters were not different between patients with moderate KOA-I, severe KOA-I, moderate KOA-S, severe KOA-S and healthy controls (supplementary Table F).

The statistical parametric mapping analysis of knee angles showed only differences between the subgroups in the knee flexion angles during terminal stance and (pre)-swing of the perturbed stride and stride after perturbation (Fig. 4). For example, patients with moderate KOA-I had higher flexion angles during 51–60%, 88–99% and 135–149% of gait cycle in response to a deceleration of one belt perturbation at intensity 3 compared to healthy controls (respectively: mean difference: 11.5°, $p < 0.01$, mean difference: 12.8°, $p < 0.01$ and mean difference: 7.5°, $p < 0.01$).

Furthermore, patients with severe KOA-I had higher flexion angles during 135–149% of gait cycle compared to healthy controls (mean difference: 9.1°, $p < 0.01$). All results of the statistical parametric mapping analysis can be found in supplementary Table G. The comparison of discrete gait parameters mainly showed higher knee flexion angles during peak swing in patients with moderate KOA-I

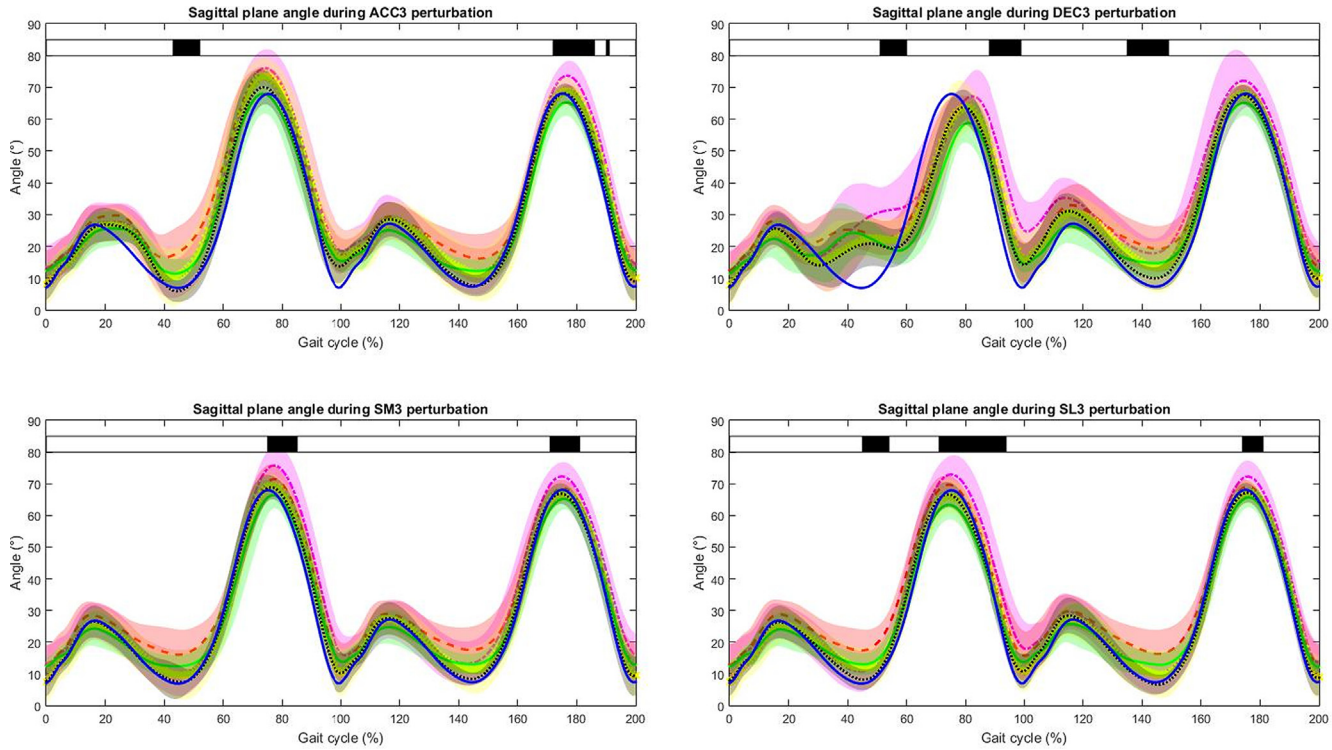

Fig. 4. Sagittal plane angles (Knee flexion angles) of perturbed stride and stride after perturbation during ACC, DEC, SL and SM perturbation intensity 3. Moderate KOA-I group (magenta, dash-dot line), severe KOA-I group (red, dashed line), moderate KOA-S group (yellow, line of crosses), severe KOA-S group (green, solid line), healthy control group perturbed (black, dotted line) and healthy control unperturbed (blue, solid line). The line represents the mean pattern of the group and the shaded area represents the standard deviation of the patterns of the group. Rectangle above graph shows significant differences (black) or not (white) between groups following from the SPM results. The control group unperturbed (blue line) was not used in the SPM analysis.

Table 3
Significant differences between the subgroups (Moderate KOA-I, Severe KOA-I, Moderate KOA-S, Severe KOA-S, Control) in the discrete gait parameters of the perturbed stride of the four different perturbation types at intensity 3. ROM = Range of motion.

Acceleration of one belt (ACC3)				
Parameter		*Groups*	*Mean difference*	*p-value*
Sagittal plane angle	Peak terminal stance	Severe KOA-I vs. Control	+10.7°	<0.01
	Peak swing	Moderate KOA-I vs. Control	+7.2°	0.01
	ROM full gait cycle	Moderate KOA-I vs. Severe KOA-S	+9.6°	0.03
Deceleration of one belt (DEC3)				
Sagittal plane angle	Peak swing	Moderate KOA-I vs. Severe KOA-S	+10°	0.01
	ROM full gait cycle	Moderate KOA-I vs. Severe KOA-S	+11.5°	0.04
Rectus femoris	Initial contact activation	Moderate KOA-S vs. Severe KOA-S	+23%	0.04
CCI medial muscles	Mean full gait cycle	Moderate KOA-I vs. Moderate KOA-S	+0.11	0.04
Sway Medial (SL3)				
Sagittal plane angle	Peak swing	Moderate KOA-I vs. Moderate KOA-S	+5.9°	<0.01
		Moderate KOA-I vs. Severe KOA-S	+8.3°	<0.01
		Moderate KOA-I vs. Control	+6.4	<0.01
	ROM full gait cycle	Moderate KOA-I vs. Severe KOA-S	+11.6°	<0.01
Sway Lateral (SM3)				
Sagittal plane angle	Peak terminal stance	Severe KOA-I vs. Control	+9.6°	0.02
	Peak swing	Moderate KOA-I vs. Moderate KOA-S	+7.3°	<0.01
		Moderate KOA-I vs. Severe KOA-S	+9.8°	<0.01
		Moderate KOA-I vs. Control	+6.8°	<0.01
		Severe KOA-I vs. Severe KOA-S	+6.1°	0.04
	ROM full gait cycle	Moderate KOA-I vs. Moderate KOA-S	+6.8°	0.03
		Moderate KOA-I vs. Severe KOA-S	+13.2°	<0.01

or during peak terminal stance in patients with severe KOA-I of the perturbed stride and stride after perturbation compared to healthy controls (Table 4 and supplementary Table H and J). Furthermore, higher ROM of the flexion angles during full gait cycle were observed in patients with moderate KOA-I compared to patients with severe KOA-I and severe KOA-S.

Some alterations in the RF, MG, MH and VM muscle activation patterns were observed in statistical parametric mapping analysis between the groups during the perturbed stride and the stride after perturbation (supplementary Table G). Moreover, few differences were present in the discrete gait parameters (Table 3, supplementary Table I and K)

3.3. Perturbation response

The perturbation responses of patients with KOA-I were in general similar to patients with KOA-S and healthy controls, because no differences in perturbation responses were observed in patients with KOA-I compared to both groups (supplementary Table I).

However, the comparison of the subgroups revealed that patients with moderate KOA-I had higher knee flexion angles perturbation response during terminal stance and pre-swing of the stride after deceleration of one belt perturbations at intensity 3 compared to the other subgroups and healthy controls (Fig. 5A and 5B). Moreover, patients with severe KOA-I showed higher CCI perturbation response during terminal stance of the sway medial perturbation at intensity 1 perturbed stride compared to patients with moderate KOA-I, moderate KOA-S and healthy controls (Fig. 5C and 5D). Details on all statistical parametric mapping analysis results of the perturbation responses are provided in supplementary table I.

4. Discussion

The aim of this study was to compare responses in neuromechanics to perturbations during gait of patients with KOA-I versus patients with KOA-S and healthy controls. Higher knee flexion angles were observed in patients with KOA-I compared to healthy controls during terminal stance and (pre-)swing of perturbed gait. The muscle activation patterns were overall similar between the groups. In response to deceleration of one belt perturbations at intensity 3, the patients with moderate KOA-I increased the knee flexion angles during terminal stance and pre-swing. In response to sway medial perturbations at intensity 1, the patients with

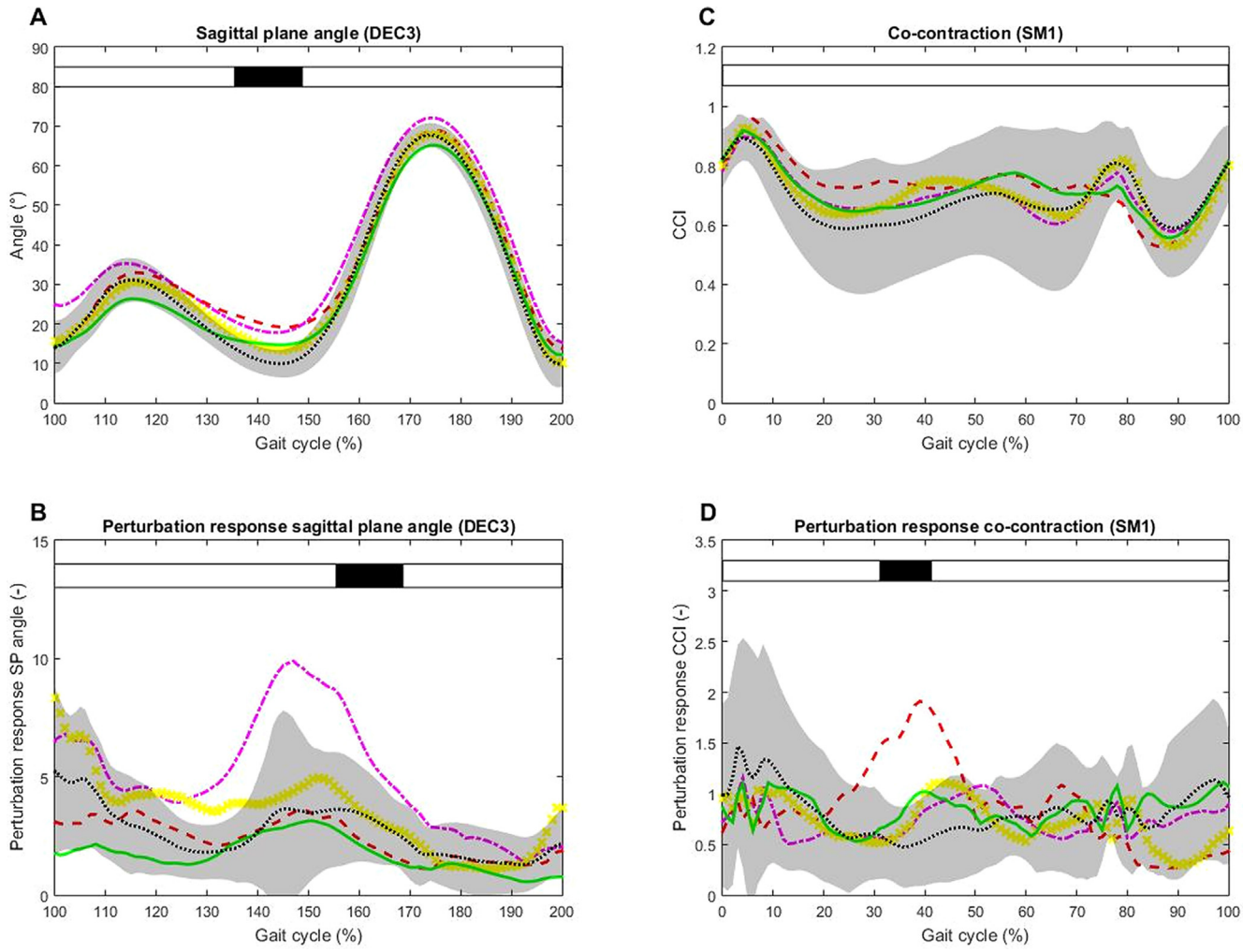

Fig. 5. The sagittal plane angles (5A) and the corresponding perturbation responses (5B) of the subgroups and controls during the stride after the DEC3 perturbation. Furthermore, the co-contraction indices (5C, quadriceps vs. hamstrings) and the corresponding perturbation responses of the co-contraction indices of the subgroups and controls during the perturbed stride of the SM1 perturbation. The subgroups were moderate KOA-I group (magenta, dash-dot line), severe KOA-I group (red, dashed line), moderate KOA-S group (yellow, line of crosses), severe KOA-S group (green, solid line) and healthy control group perturbed (black, dotted line). The line represents the mean pattern of the group and the shaded area represents the standard deviation of the patterns of the control group. Rectangle above graph shows significant differences (black) or not (white) between all groups following from the SPM results.

severe KOA-I increased co-contraction of the thigh muscles (quadriceps vs. hamstrings) during terminal stance. These responses in neuromechanics could be distinct for patients with knee joint instability, have consequences for the progression of KOA and assist in the assessment of knee joint instability.

Walking with high knee flexion angles during terminal stance could be a distinct strategy for patients with KOA-I. A study by Fuentes et al. observed similar results in patients with anterior cruciate ligament injury during a comfortable and fast walking condition (Fuentes et al., 2011). They described this alteration as "pivot-shift avoidance gait" and stated that patients possibly do this to avoid situations where their knee joints are at risk of anterolateral rotatory instability (i.e. full knee extension). In our study especially patients with severe KOA-I presented high flexion angles during terminal stance of perturbed gait, as well as for unperturbed gait. In contrast, all other subjects only presented higher flexion angles during terminal stance of the deceleration of one belt perturbations at intensity 3 (mentioned by the subjects as the most challenging perturbation). Interestingly, all subjects recovered during the stride after the deceleration of one belt perturbations at intensity 3, except for the patients with moderate KOA-I who still showed high flexion angles during terminal stance and pre-swing (Fig. 5). This suggests that a high knee flexion angle during terminal stance is an indicator of knee joint instability and, depending on (radiographic) disease severity, a different type of perturbation is needed to evoke this response.

Increasing co-contraction of the thigh muscles could be a method of patients with KOA-I to stiffen up the joint to try to actively stabilize the knee in response to the perturbations. This is at the expense of an increase in internal load on the knee joint, leading to elevated stresses on the cartilage (Hodges et al., 2016). Similar to the results of this study, Schmitt et al (Schmitt and Rudolph, 2008) also observed higher co-contraction in the medial muscles of patients with KOA-I, but then during weight acceptance during a lateral perturbation (terminal stance not reported). Besides the increase in co-contraction in this study, not many other differences were observed in the responses of the individual muscle activation patterns to perturbations. This is in agreement with other studies investigating muscle activation of KOA patients during perturbed gait (Baker et al., 2019; Kumar et al., 2014). One reason for this could be that each patient adapts their muscles in their own way, creating heterogeneous responses. Another reason could be that surface EMG is not sensitive enough to show the differences between the groups. Future studies with larger sample sizes could shed light on the contribution of individual muscles to knee joint instability and the role of co-contraction.

The observed responses in neuromechanics in patients with KOA-I could be used to objectively assess knee joint instability during gait using the scheme presented in Fig. 6. This scheme follows the conceptual definition for dynamic knee joint stability in which a patient is defined instable if he or she does not have the capacity (ability to do a particular thing) to respond to a perturbation during gait within the natural boundaries of the knee joint (defined by healthy control group) (Schrijvers et al., 2019). In this case, a patient was identified as instable if he or she had a higher CCI perturbation response (quads vs. hamstrings) during terminal stance (30–50% gait cycle) than the maximum CCI perturbation response observed in healthy controls in response to a sway medial perturbation at intensity 1. Furthermore, a patient was also identified instable if he or she had higher knee flexion angles during terminal stance, initial contact or peak swing than the maximum values observed in healthy controls during the stride after the deceleration of one belt perturbation at intensity 3. Based on the responses in neuromechanics to perturbations, 85% of the patients were correctly identified as "Instable" or "Stable" of the pre-determined groups based on self-reported instability. Of the remaining 15% of the patients, two patients were identified as "Stable" while reporting "Instable" and four patients were identified as "Instable" while reporting "Stable". This shows that alterations in neuromechanics could be used to assess knee joint instability. Furthermore, we think that the concept of knee joint instability is better represented by a continuum scale instead of dichotomous scale, as also suggested by Nguyen et al. (Nguyen et al., 2011). Objective assessment based on alterations in neuromechanics could then assist in determining on what level of instability a patient is and identify the neuromechanics that need to be treated. For example, if a patients walks with higher knee flexion angles than healthy control subjects during perturbed gait, treatment could focus on regaining normal knee flexion angles in order to improve stability of the joint and possibly delay knee OA progression (Blalock et al., 2015b; Favre et al., 2016). Future studies are needed to confirm these hypothetical mechanisms. Moreover, exploration of gait perturbations (timing, duration) could assist in finding more responses in neuromechanics particular for patients with KOA-I.

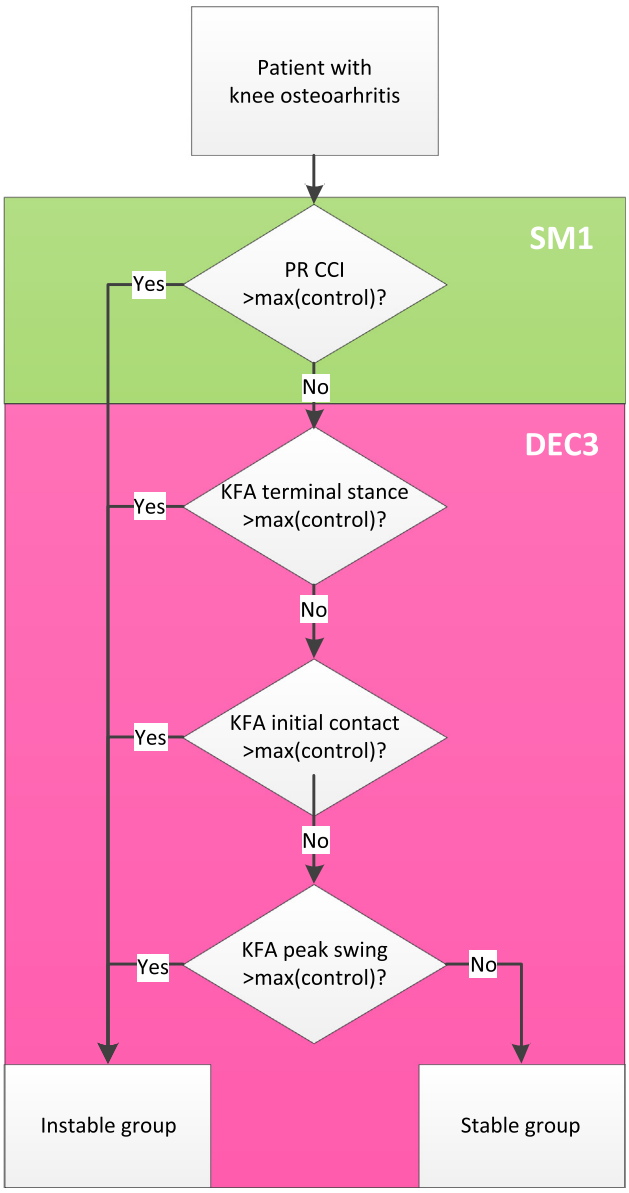

Fig. 6. An assessment scheme to identify if a patient has objective knee joint instability during gait or not. KFA: Knee flexion angle, PR: Perturbation response and CCI: Co-contraction index (quadriceps vs. hamstrings).

This study has some limitations. First, skin-based markers were used to measure knee kinematics and therefore actual knee joint instability might be obscured by skin movement artefacts. Second, in literature many different methods are used to report knee joint instability, so the method used to divide the groups based on self-reported knee joint instability could have influenced the results. Thirdly, patients could have experienced fear or fatigue during the measurement. Instructions on the safety measures and a break between the perturbation trials were provided in order to reduce such effect.

5. Conclusion

Patients with self-reported knee joint instability (KOA-I) responded to perturbations during gait with higher knee flexion angles, increased co-contraction of muscles or both during terminal stance compared to patients reporting stable knees (KOA-S) and healthy controls. These alterations in neuromechanics were found to be distinct for patients with knee joint instability and could therefore be used to assess knee joint instability and better target treatments to improve stability of the joint. Furthermore, the consequences of altered neuromechanics due to instability on the development of KOA are unknown and therefore need to be investigated.

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Conflict of interest statement

The authors confirm that there are no conflicts of interests regarding the work described in the current manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbiomech.2021.110325.

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